Answer 1:

Bibliographic Information

Phase I and pharmacodynamic trial of the DNA methyltransferase inhibitor decitabine and carboplatin in solid tumors. Appleton, Kim; Mackay, Helen J.; Judson, Ian; Plumb, Jane A.; McCormick, Carol; Strathdee, Gordon; Lee, Chooi; Barrett, Sophie; Reade, Sarah; Jadayel, Dalal; Tang, Adrian; Bellenger, Katharine; Mackay, Lynsay; Setanoians, Albert; Schatzlein, Andreas; Twelves, Chris; Kaye, Stanley B.; Brown, Robert. Centre for Oncology and Applied Pharmacology, Cancer Research UK Beatson Laboratories, Glasgow University, Glasgow, UK. Journal of Clinical Oncology (2007), 25(29), 4603-4609. Publisher: American Society of Clinical Oncology, CODEN: JCONDN ISSN: 0732-183X. Journal written in English. CAN 148:159114 AN 2007:1282019 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: The DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine (decitabine) induces DNA demethylation and re-expression of epigenetically silenced genes, and increases carboplatin sensitivity of tumor xenograft models. We designed a clin. study to det. the feasibility of delivering a dose of decitabine, combined with carboplatin, that would be capable of producing equiv. biol. effects in patients with solid tumors. Patients and Methods: In a two-stage design, 33 patients received escalating doses of decitabine administered as a 6-h infusion on day 1 followed by carboplatin, area under the concn.-time curve (AUC) 5 (cohort 1) and AUC 6 (cohort 2), on day 8 of a 28-day cycle. Pharmacodynamic analyses included 5-methyl-2'-deoxycytidine levels, MAGE1A CpG island methylation, and fetal Hb (HbF) expression. Results: The major toxicity was myelosuppression. Dose limiting toxicities, prolonged grade 4 neutropenia (one patient), and sepsis and grade 3 anorexia/fatigue (one patient), were seen in two of four patients treated with decitabine 135 mg/m2 and carboplatin AUC 5. Dose limiting toxicity comprising neutropenic sepsis (one patient) and grade 3 fatigue (one patient) was seen in two of 10 patients treated at decitabine 90 mg/m2 and carboplatin AUC 6. Decitabine induced dose-dependent, reversible demethylation in peripheral-blood cells (PBCs) maximally at day 10. Furthermore, decitabine 90 mg/m2 induced demethylation of the MAGE1A CpG island in PBCs, buccal cells, and tumor biopsies, as well as elevation of HbF expression. Conclusion: Decitabine can be combined safely with carboplatin at a dose and schedule that causes epigenetic changes equiv. to or greater than that obsd. in mice with carboplatin-sensitized xenografts. The recommended dose/schedule for phase II trials is decitabine 90 mg/m2 (day 1) followed by carboplatin AUC 6 (day 8) every 28 days.

Answer 2:

Bibliographic Information

Combining epigenetic and cytotoxic therapy in the treatment of solid tumors. Plimack, Elizabeth R.; Stewart, David J.; Issa, Jean-Pierre J. The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. Journal of Clinical Oncology (2007), 25(29), 4519-4521. Publisher: American Society of Clinical Oncology, CODEN: JCONDN ISSN: 0732-183X. Journal; General Review written in English. CAN 148:134704 AN 2007:1282001 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. The research of Appleton et al. (2007) entitled "Phase I and pharmacodynamic trial of the DNA methyltransferase inhibitor decitabine and carboplatin in solid tumors" is reviewed with commentary and refs. Appleton et al. conducted trial combining decitabine and carboplatin in advanced solid tumors. This dose-finding trial uses a series of doses of decitabine that, per cycle, all fall within the range of low doses shown to induce hypomethylation in vitro and in vivo. Furthermore, decitabine was administered 8 days before initiation of cytotoxic therapy, in keeping with preclin. models. The investigators conducted two sep. dose escalations of decitabine, the first with carboplatin fixed at area under the concn. time curve (AUC) 5 and the second at AUC 6, concluding that the recommended phase II dosing for this combination is decitabine 90 mg/rn2 administered on day 1 followed by carboplatin AUC 6 on day 8 of a 28-day cycle. Of the 30 patients assessable for response, one patient with melanoma had a partial response and three other patients had stable disease. The majority of responses clustered at the recommended combination dose.

Answer 3:

Bibliographic Information

Dexamethasone as a chemosensitizer for breast cancer chemotherapy: potentiation of the antitumor activity of adriamycin, modulation of cytokine expression, and pharmacokinetics. Wang, Hui; Wang, Ying; Rayburn, Elizabeth R.; Hill, Donald L.; Rinehart, John J.; Zhang, Ruiwen. Division of Clinical Pharmacology, Department of Pharmacology and Toxicology, Gene Therapy Center, University of Alabama at Birmingham, Birmingham, AL, USA. International Journal of Oncology (2007), 30(4), 947-953. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 147:1122 AN 2007:421268 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Dexamethasone (DEX) is mainly used as an antiemetic agent in cancer therapy. We have recently demonstrated that DEX pretreatment increases the antitumor activity of the cancer chemotherapeutic agents carboplatin and gemcitabine, and decreases host toxicity in nude mouse xenograft models of human cancer. However, the underlying mechanisms are not fully understood. The present study was designed to det. the effects of DEX pretreatment on the anticancer activity of adriamycin (ADR) in a syngeneic model of breast cancer (4T1), emphasizing the effects of DEX on cytokine expression and modulation of ADR pharmacokinetics. We have demonstrated five major new findings about DEX pretreatment: (a) it enhances the therapeutic effect of ADR, inducing almost complete inhibition of tumor growth; (b) it increases tumor ADR accumulation; (c) it modulates the expression of cytokines produced by the tumor, increasing TNFα and decreasing IL-1β and VEGF expression; (d) it enhances the effects of ADR on induction of apoptosis and inhibition of cell proliferation; and (e) it suppresses nuclear NFκB activation and inhibits ADR-induced NFκB activation, possibly via IκB up-regulation. These findings suggest that DEX can be used as a chemosensitizer and chemoprotectant. These results provide a rationale for the expanded clin. use of DEX for cancer therapy.

Answer 4:

Bibliographic Information

Effect of 2-(8-hydroxy-6-methoxy-1-oxo-1H-2-benzopyran-3-yl) propionic acid in combination with carboplatin on gastric carcinoma growth in vivo. Chen, Jin-Lian; Zhu, Jin-Shui; Hong, Jing; Chen, Ming-Xiang; Lu, Jin-Lai; Chen, Wei-Xiong; Shen, Bo; Zhu, Zu-Ming; Chen, Ni-Wei. Department of Gastroenterology, Shanghai Sixth People's Hospital, Shanghai Jiaotong University, Shanghai, Peop. Rep. China. World Journal of Gastroenterology (2007), 13(4), 509-514. Publisher: World Journal of Gastroenterology, CODEN: WJGAF2 ISSN: 1007-9327. Journal written in English. CAN 146:350815 AN 2007:271775 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Aim: To investigate the effects of 2-(8-hydroxy-6-methoxy-1-oxo-1H-2-benzopyran-3-yl) propionic acid (NM-3) alone and in combination with carboplatin on tumor growth and apoptosis in mouse models of human gastric cancer constructed by s.c. implantation of histol. intact tumor tissue. Methods: Human gastric cancer SGC-7901 tissues were implanted into the dorsal subcutis of nude mice. One week after tumors reached to a vol. of 50-100 mm3 for around 1 wk, these mice were randomly divided into 8 groups (n = 10). NM-3 was injected peritoneally at the dose of 10 mg/kg, 20 mg/kg or 40 mg/kg every other day for 5 wk, combined with carboplatin (5 mg/kg) every third day for 4 wk. As controls of combined treatment, another 4 groups of mice were injected with either NM-3 at 10 mg/kg, 20 mg/kg or 40 mg/kg, or with carboplatin alone (5 mg/kg). The control mice received normal saline. Tumor wt., tumor growth inhibition (TGI), and intratumoral microvessel d. (MVD) were evaluated. Apoptosis of human gastric cancer was detected by TUNEL method and flow cytometry anal., resp. Results: The mean tumor vol. (692.40 $\pm$ 58.43 mm3, 548.30 $\pm$ 66.02 mm3, 382.13 $\pm$ 43.52 mm3) after treatment with carboplatin combined NM-3 at the dose of 10 mg/kg, 20 mg/kg or 40 mg/kg was lower than that after treatment with either NM-3 at the dose of 10 mg/kg, 20 mg/kg or 40 mg/kg or with carboplatin alone. Compared with the normal saline group, NM-3 administered at 10 mg/kg, 20 mg/kg or 40 mg/kg significantly reduced the tumor wt. in these groups ($P < 0.05$). Carboplatin used alone at 5 mg/kg showed minimal effects. But NM-3 in combination with carboplatin had greater effects of tumor wt. than either NM-3 or carboplatin alone. NM-3 alone at the dose 10 mg/kg or in combination with carboplatin had no obvious effects on body changes. Two mice died of diarrhea in each of the two groups treated with 40 mg/kg NM-3 or with 40 mg/kg NM-3 in combination with carboplatin. A significant increase in apoptosis was obsd.

in the NM-3 treated groups, and the effect was more significant in the groups treated with carboplatin in combination with NM-3 at 10 mg/kg, 20 mg/kg and 40 mg/kg, than in the control group. The induction of apoptosis was pos. assocd. with the dose of NM-3. NM-3 significantly reduced the neo-microvascular formation of gastric cancer. The MVD was lower in the groups treated with NM-3 or with NM-3 in combination with carboplatin than in the group treated with carboplatin or in the normal saline group ($P < 0.05$). Conclusion: The results suggest that the inhibitory effect of NM-3 on gastric cancer growth is mediated through decreased angiogenesis and the increased induction of apoptosis. Furthermore, NM-3 alone at the dose of 10 mg/kg or in combination with carboplatin has no obvious effects on body changes, indicating that NM-3 in combination with carboplatin may be effective in the treatment of gastric cancer. The toxicity of NM-3 needs further studies.

Answer 5:

Bibliographic Information

Tumor growth inhibition with cetuximab and chemotherapy in non-small cell lung cancer xenografts expressing wild-type and mutated epidermal growth factor receptor. Steiner, Philipp; Joynes, Christopher; Bassi, Rajiv; Wang, Su; Tonra, James R.; Hadari, Yaron R.; Hicklin, Daniel J. ImClone Systems Incorporated, New York, NY, USA. Clinical Cancer Research (2007), 13(5), 1540-1551. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:22955 AN 2007:230062 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Targeting the epidermal growth factor receptor (EGFR) is a validated approach to treat cancer. In non-small cell lung cancer (NSCLC), EGFR contains somatic mutations in 10% of patients, which correlates with increased response rates to small mol. inhibitors of EGFR. We analyzed the effects of the monoclonal IgG1 antibody Erbitux (cetuximab) in NSCLC xenografts with wild-type (wt) or mutated EGFR. NSCLC cell lines were grown s.c. in nude mice. Dose-dependent efficacy was established for cetuximab. To det. whether combination therapy produces tumor regressions, cetuximab was dosed at half-maximal efficacy with chemotherapy used at max. tolerated dose. Cetuximab showed antitumor activity in wt (A549, NCI-H358, NCI-H292) and mutated [HCC-827 (delE746-A750), NCI-H1975 (L858R, T790M)] EGFR-expressing xenografts. In the H292 model, cetuximab and docetaxel combination therapy was more potent to inhibit tumor growth than cetuximab or docetaxel alone. Cisplatin augmented efficacy of cetuximab to produce 6 of 10 regressions, whereas 1 of 10 regressions was found with cetuximab and no regression was found with cisplatin. Using H1975 xenografts, gemcitabine increased efficacy of cetuximab resulting in 12 of 12 regressions. Docetaxel with cetuximab was more efficacious with seven of nine regressions compared with single treatments. Cetuximab inhibited autophosphorylation of EGFR in both H292 and H1975 tumor lysates. Exploring the underlying mechanism for combination effects in the H1975 xenograft model, docetaxel in combination with cetuximab added to the antiproliferative effects of cetuximab but was the main component in this drug combination to induce apoptosis. Cetuximab showed antitumor activity in NSCLC models expressing wt and mutated EGFR. Combination treatments increased the efficacy of cetuximab, which may be important for the management of patients with chemorefractory NSCLC.

Answer 6:

Bibliographic Information

Effect of cinnamaldehyde on proliferation and apoptosis of a heterologous graft in nude mice bearing human gastric carcinoma. Huang, Jing-Qun; Wang, Si-Wang; Luo, Xiao-Xing; Xie, Yan-Hua. Inst. Materia Medica, Fourth Military Med. Univ., Xian, Peop. Rep. China. Jiefangjun Yaoxue Xuebao (2006), 22(5), 343-346. Publisher: Zhongguo Renmin Jiefangjun Zonghouqinbu Weishengbu Yaopin Yiqi Jianyansuo, CODEN: JYXIAY ISSN: 1008-9926. Journal written in Chinese. CAN 147:63439 AN 2006:1331903 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The cytotoxic effects of Cinnamaldehyde (CA) on cancer cell lines and effects on proliferation and apoptosis of heterologous graft in

nude mice bearing human gastric carcinoma was investigated. The anti-proliferative effects of CA in seven human cancer cell lines were tested by MTT assay. The model of nude mice bearing developed xenografts of the SGC-7901 cell line were established and administered with different dose of CA and Carboplatin (CBP) by i.p. injection (i.p.). The wts. of the tumors and inhibitory rate of tumors of the mice were obsd. The changes of SGC-7901 cell cycle of transplanted tumor and apoptosis rate were detd. by flow cytometry (FCM). The morphol. changes of apoptosis were obsd. by transillumination electron microscope (TEM). In vitro studies showed that CA could inhibit tumor growth in seven human cancer cells lines in a concn.-dependent manner, and the IC50 values ranged from 12.3 to 37.1 μg·ml-1. In tumor bearing mice, CA and CBP, administered (i.p.) once daily for 21 days, clearly prevented tumor growth in nude mice. The inhibitory rate of CA at 50, 100 mg·kg-1 and CBP 5 mg·kg-1 group was 15.15 %, 41.67 %, 60.61 % and 65.15% resp. The no. of cells in the S phase of CA treatment increased. Compared with Saline, the apoptosis rate of CA in the 50, 100mg·kg-1 group increased significantly ($P<0.05$ and $P<0.01$). The human gastric carcinoma xenografts in nude mice treated by CA showed significant morphol. changes in different apoptotic phases. It was concluded that CA has obvious antitumor effects in vivo and the mechanism relates to proliferation inhibited and induction of apoptosis in cancer cells.

Answer 7:

Bibliographic Information

Preclinical Characterization of AEG35156/GEM 640, a Second-Generation Antisense Oligonucleotide Targeting X-Linked Inhibitor of Apoptosis. LaCasse, Eric C.; Cherton-Horvat, Gabriele G.; Hewitt, Kimberley E.; Jerome, Lori J.; Morris, Stephen J.; Kandimalla, Ekambar R.; Yu, Dong; Wang, Hui; Wang, Wei; Zhang, Ruiwen; Agrawal, Sudhir; Gillard, John W.; Durkin, Jon P. Aegera Therapeutics, Inc., Montreal, QC, Can. Clinical Cancer Research (2006), 12(17), 5231-5241. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:454298 AN 2006:899348 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Cancer cells can use X-linked inhibitor of apoptosis (XIAP) to evade apoptotic cues, including chemotherapy. The antitumor potential of AEG35156, a novel second-generation antisense oligonucleotide directed toward XIAP, was assessed in human cancer models when given as a single agent and in combination with clin. relevant chemotherapeutics. Exptl. Design: AEG35156 was characterized for its ability to cause dose-dependent redns. of XIAP mRNA and protein in vitro and in vivo, to sensitize cancer cell lines to death stimuli, and to exhibit antitumor activity in multiple human cancer xenograft models as a single agent or in combination with chemotherapy. RESULTS: AEG35156 reduced XIAP mRNA levels with an EC50 of 8 to 32 nmol/L and decreased XIAP protein levels by >80%. Loss of XIAP protein correlated with increased sensitization to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis in Panc-1 pancreatic carcinoma cells. AEG35156 exhibited potent antitumor activity relative to control oligonucleotides in three human cancer xenograft models (prostate, colon, and lung) and was capable of inducing complete tumor regression when combined with taxanes. Antitumor effects of AEG35156 correlated with suppression of tumor XIAP levels. CONCLUSIONS: AEG35156 reduces XIAP levels and sensitizes tumors to chemotherapy. AEG35156 is presently under clin. assessment in multiple phase I trials in cancer patients as a single agent and in combination with docetaxel in solid tumors or cytarabine/idarubicin in leukemia.

Answer 8:

Bibliographic Information

Molecular mechanism of phenoxodiol-induced apoptosis in ovarian carcinoma cells. Alvero, Ayesha B.; O'Malley, David; Brown, David; Kelly, Graham; Garg, Manish; Chen, Wei; Rutherford, Thomas; Mor, Gil. Department of Obstetrics & Gynecology, Yale University School of Medicine, New Haven, CT, USA. Cancer (Hoboken, NJ, United States) (2006), 106(3), 599-608. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 145:76157 AN 2006:155201 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Previously, it was demonstrated that phenoxodiol induces apoptosis in epithelial ovarian carcinoma (EOC) cells and that it is capable of sensitizing these cells to Fas-mediated apoptosis. The objectives of this study were to det. whether phenoxodiol can also act as chemosensitizer to chemotherapeutic agents and to characterize the mol. mechanism behind its sensitizing effect. Ten EOC cell lines were used in this study. The effect of phenoxodiol on the inhibitory concn. 50% (IC50) of carboplatin, paclitaxel, and gemcitabine was detd. by the CellTiter 96 Assay. The in vivo effect of combination treatments with phenoxodiol and the above-mentioned agents was detd. in animal xenograft models. Apoptosis was measured using the Caspase-Glo Assay and the apoptotic cascade was characterized by Western blot analyses. The results showed that phenoxodiol is able to sensitize EOC cells to carboplatin, paclitaxel, and gemcitabine both in vitro and in vivo. In addn., it was demonstrated that phenoxodiol is capable of inducing apoptosis by: (1) the activation of the mitochondrial pathway through caspase-2 and Bid signaling, and (2) the proteasomal degrdn. of the anti-apoptotic protein XIAP. Understanding the components of the apoptotic pathway activated by phenoxodiol, which allows it to sensitize EOC cells to chemotherapeutic agents, will provide valuable information on the characteristic mode of action of a chemosensitizer. This will help in the identification of novel drugs and in the design of better strategies for combination therapy in patients with recurrent ovarian carcinoma.

Answer 9:

Bibliographic Information

Preclinical anti-tumor activity of XR5944 in combination with carboplatin or doxorubicin in non-small-cell lung carcinoma. Harris, Susan M.; Scott, John A.; Brown, Jeffrey L.; Charlton, Peter A.; Mistry, Prakash. Xenova Ltd, Slough, Xenova Ltd, Slough, Berkshire, UK. Anti-Cancer Drugs (2005), 16(9), 945-951. Publisher: Lippincott Williams & Wilkins, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 143:339168 AN 2005:997956 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

XR5944 (MLN944) is a novel bis-phenazine currently in phase I clin. trials that has demonstrated potent cytotoxic activity against a variety of tumor models. The combinations of XR5944 with carboplatin or doxorubicin were investigated in COR-L23/P human non-small-cell lung carcinoma (NSCLC) cells in vitro and the corresponding xenografts in vivo. In vitro cytotoxicity was evaluated by the sulforhodamine B assay and the drug interactions following simultaneous or sequential exposure were detd. using median-effect anal. to calc. combination indexes (CIs). XR5944 demonstrated potent cytotoxicity compared to either carboplatin or doxorubicin in COR-L23/P cells. Simultaneous or sequential exposure of XR5944 followed by carboplatin led to a synergistic response (CI<1), whereas the reverse order of addn. showed an additive or antagonistic response (CI≤1). Sequential administration of doxorubicin followed by XR5944 demonstrated marginally improved cytotoxicity (CI=1.31-0.77) than other schedules (CI=1.50-1.22) relative to individual drugs. Anti-tumor activity against COR-L23/P xenografts in nude mice was enhanced by administration of XR5944 (2 or 5 mg/kg) immediately before carboplatin (50 mg/kg) compared to single-agent treatment at the same doses. Improved efficacy was also obsd. by sequential administration of 7 mg/kg doxorubicin 48 h before 2.5 or 5 mg/kg XR5944. No addnl. toxicity was obsd. with combinations compared to single-agent treatment alone as detd. by body wts. These data suggest that combinations of XR5944 with carboplatin or doxorubicin are of significant interest for clin. use, and that the schedule of administration may be important for achieving clin. efficacy over single-agent therapy.

Answer 10:

Bibliographic Information

Synergistic interaction between platinum-based antitumor agents and demethylcantharidin. To, Kenneth K. W.; Ho, Yee-Ping; Au-Yeung, Steve C. F. School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, Peop. Rep. China. Cancer Letters (Amsterdam, Netherlands) (2005), 223(2), 227-237. Publisher: Elsevier B.V., CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 143:125820 AN 2005:425268 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A novel series of TCM-platinum complexes [Pt(C8H8O5)(NH2R)2], designed from incorporating demethylcantharidin, a modified component from a traditional Chinese medicine (TCM) with a platinum moiety was found to circumvent cisplatin resistance in mouse leukemia and human hepatocellular carcinoma. These properties are most likely due to the inclusion of the protein phosphatase 2A (PP2A)-inhibiting demethylcantharidin in the novel compds. We have investigated the potential synergistic effect of combining demethylcantharidin with a platinum-based antitumor agent, such as cisplatin, carboplatin, or oxaliplatin in vitro against L1210 mouse leukemia and SK-Hep-1 human hepatocellular carcinoma, and in vivo against a SK-Hep-1 s.c.-inoculated xenograft in nude mice, using median effect anal. Demethylcantharidin and the platinum antitumor agents were synergistic in all cell lines tested in vitro, and the most effective antiproliferative regimen was when demethylcantharidin was added 24 h before cisplatin. Synergistic antitumor activity was also demonstrated in vivo without undue toxicity; no excessive loss in mouse body wt. or overt pathol. were obsd. at the EDs. The results support a new approach for augmenting cytotoxic effect of established Pt-based drugs with demethylcantharidin in treating human hepatocellular carcinoma and other solid tumors.

Answer 11:

Bibliographic Information

Targeting mammalian target of rapamycin synergistically enhances chemotherapy-induced cytotoxicity in breast cancer cells. Mondesire, Wallace H.; Jian, Weiguo; Zhang, Haixia; Ensor, Joe; Hung, Mien-Chie; Mills, Gordon B.; Meric-Bernstam, Funda. Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. Clinical Cancer Research (2004), 10(20), 7031-7042. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:190488 AN 2004:975688 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The serine-threonine kinase mammalian target of rapamycin has emerged as a potential target for cancer therapy. Rapamycin and rapamycin analogs are undergoing clin. trials and have induced clin. responses in a subgroup of patients. Rapamycin has also been reported to enhance the efficacy of several cytotoxic agents. The aim of this study was to det. the nature of the interactions between rapamycin and chemotherapeutic agents used as first- and second-line agents against breast cancer. We performed a multiple drug effect/combination index isobologram anal. in cells sensitive and resistant to rapamycin alone in vitro, and we evaluated the in vivo efficacy of combination therapy in a rapamycin-sensitive model. In vitro, synergistic interactions were obsd. in combinations with paclitaxel, carboplatin, and vinorelbine. Additive effects were obsd. in combinations with doxorubicin and gemcitabine. Rapamycin dramatically enhanced paclitaxel- and carboplatin-induced apoptosis. This effect was sequence dependent and mediated at least partly through caspase activation. Furthermore, rapamycin enhanced chemosensitivity to paclitaxel and carboplatin in HER2/neu-overexpressing cells, suggesting a potential approach to these poorly behaving tumors. Cell lines that are resistant to the growth-inhibitory effect of rapamycin were also resistant to rapamycin-mediated chemosensitization. In vivo, rapamycin combined with paclitaxel resulted in a significant redn. in tumor vol. compared with either agent alone in rapamycin-sensitive tumors. Rapamycin potentiates the cytotoxicity of selected chemotherapeutic agents in cell lines sensitive to the effects of rapamycin due to aberrations in the phosphatidylinositol 3'-kinase/Akt pathway, suggesting that combination therapy may be effective in patients selected for aberrations in this pathway.

Answer 12:

Bibliographic Information

Synthesis and Biological Activity of Water-Soluble Maleimide Derivatives of the Anticancer Drug Carboplatin Designed as Albumin-Binding Prodrugs. Warnecke, Andre; Fichtner, Iduna; Garmann, Dirk; Jaehde, Ulrich; Kratz, Felix. Tumor Biology Center, Freiburg, Germany. Bioconjugate Chemistry (2004), 15(6), 1349-1359. Publisher: American Chemical Society, CODEN: BCCHES ISSN: 1043-1802. Journal written in English. CAN 142:79772 AN 2004:885946 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Four platinum(II) complexes were synthesized by reacting either [Pt trans-DACH](NO3)2 with a 6-maleimidocaproic acid, a 15-maleimido-4,7,10,13-tetroxapentadecanoic acid, and a 6-maleimido-4-oxacaproic ester deriv. of cyclobutane-1,1-dicarboxylic acid (CBDA) or [Pt(NH3)2](NO3)2 with a 6-maleimido-4-oxacaproic ester deriv. of CBDA. Both complexes contg. the 6-maleimido-4-oxacaproic ester showed good water soly. (≥8 mg/mL) and CE expts. revealed rapid binding to human serum albumin and the formation of biadducts with dGMP and dAMP. In the MaTu xenograft model in nude mice, both complexes showed an improved antitumor effect at their max. tolerated dose (2 × 50 mg/kg carboplatin equiv.) compared to therapy with carboplatin at equimolar dose or at its optimal dose (2 × 75 mg/kg).

Answer 13:

Bibliographic Information

Distinct Responses of Xenografted Gliomas to Different Alkylating Agents Are Related to Histology and Genetic Alterations. Leuraud, Pascal; Taillandier, Luc; Medioni, Jacques; Aguirre-Cruz, Lucinda; Criniere, Emmanuelle; Marie, Yannick; Kujas, Michele; Golmard, Jean-Louis; Duprez, Adrien; Delattre, Jean-Yves; Sanson, Marc; Poupon, Marie-France. Institut National de la Sante et de la Recherche Medicale, Laboratoire de Biologie des Interactions Neurones-Glie, Groupe Hospitalier Pitie-Salpetriere, Paris, Fr. Cancer Research (2004), 64(13), 4648-4653. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 141:116709 AN 2004:537842 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A series of 12 human gliomas was established as xenografts in nude mice and used to evaluate the relationship between histol., genetic parameters, and response to alkylating agents. Eight were high-grade oligodendroglial tumors, and four were glioblastoma. They were characterized for their genetic alterations, including those considered as "early" alterations, namely loss of chromosome 1 ± loss of chromosome 19q, TP53 mutation, and those considered as "late" alterations, namely loss of chromosome 10, loss of chromosome 9p, EGFR genomic amplification, PTEN mutation, CDKN2A homozygous deletion, and telomerase reactivation. Chemosensitivity of xenografts to four alkylating agents, temozolomide (42 mg/kg, days 1-5, p.o.), 1,3-bis(2-chloroethyl)-1-nitrosourea (5 mg/kg, day 1, i.p.), Ifosfamide (90 mg/kg, days 1-3, i.p.), and carboplatin (66 mg/kg, day 1, i.p.) was tested by administration of drugs to tumor-bearing mice. Although each tumor presented an individual response pattern, glioblastoma had a lower chemosensitivity than oligodendrogliomas, and temozolomide was the most effective drug. Deletion of 1p ± 19q was assocd. with higher chemosensitivity, whereas late mol. alterations, particularly EGFR amplification, were assocd. with chemoresistance. These results suggest that the combined use of histol. and mol. markers should eventually be helpful selecting the most appropriate agents for treatment of malignant oligodendrogliomas and astrocytomas.

Answer 14:

Bibliographic Information

Pretreatment with dexamethasone increases antitumor activity of carboplatin and gemcitabine in mice bearing human cancer Xenografts: in vivo activity, pharmacokinetics, and clinical implications for cancer chemotherapy. Wang, Hui; Li, Mao; Rinehart, John J.; Zhang, Ruiwen. Department of Pharmacology and Toxicology, Division of Clinical Pharmacology, University of Alabama at Birmingham, Birmingham, AL, USA. Clinical Cancer Research (2004), 10(5), 1633-1644. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:307750 AN 2004:194636 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The present study was undertaken to det. the effects of dexamethasone (DEX) pretreatment on antitumor activity and pharmacokinetics of the cancer chemotherapeutic agents carboplatin and gemcitabine. Antitumor activities of carboplatin and gemcitabine with or without DEX pretreatment were detd. in six murine-human cancer xenograft models, including cancers of colon (LS174T), lung (A549 and H1299), and breast (MCF-7 and MDA-MB-468) and glioma (U87-MG). Effects of DEX on plasma and tissue pharmacokinetics of carboplatin and gemcitabine were also detd. by using the LS174T, A549, and H1299 models. Although DEX alone

showed minimal antitumor activity, DEX pretreatment significantly increased the efficacy of carboplatin, gemcitabine, or a combination of both drugs by 2-4-fold in all xenograft models tested. Without DEX treatment, the tumor exposure to carboplatin, measured by the area under the curve, was markedly lower than normal tissues. However, DEX pretreatment significantly increased tumor carboplatin levels, including 200% increase in area under the curve, 100% increase in max. concn., and 160% decrease in clearance. DEX pretreatment similarly increased gemcitabine uptake in tumors. .To our knowledge, this is the first report that DEX significantly enhances the antitumor activity of carboplatin and gemcitabine and increases their accumulation in tumors. These results provide a basis for further evaluation of DEX as a chemosensitizer in patients.

Answer 15:

Bibliographic Information

Improved targeting of platinum chemotherapeutics the antitumor activity of the HPMA copolymer platinum agent AP5280 in murine tumour models. Lin, X.; Zhang, Q.; Rice, J. R.; Stewart, D. R.; Nowotnik, D. P.; Howell, S. B. Department of Medicine and the Cancer Center, University of California, La Jolla, CA, USA. European Journal of Cancer (2004), 40(2), 291-297. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 141:150527 AN 2004:34766 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

AP5280 is a novel N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-bound platinum (Pt) therapeutic designed to increase the therapeutic index relative to conventional, small-mol. platinum agents. The platinum-polymer construct accumulates in solid tumors on the basis of increased capillary permeability. The bound platinum moiety is present as an N,O-Pt chelate at the distal end of a tetrapeptide linker, glycine-phenylalanine-leucine-glycine, and the wt.-av. mol. wt. (Mw) of the construct is 22 kDa. The antitumor activity and toxicity of AP5280 were assessed in the syngeneic murine B16F10 and Lewis lung tumor models, and in the human ovarian carcinoma 2008 and head and neck squamous carcinoma UMSCC10b xenograft models. The max. tolerated dose (MTD) of AP5280 was 6-fold greater than that of carboplatin (CBDCA) in vivo. AP5280 was active in all four tumor models, and it displayed a higher therapeutic index than CBDCA in each of these tumor models. The antitumor effect of AP5280 given at 16% of its MTD was equiv. to that produced by a MTD of CBDCA. Thus, consistent with the design goal for this drug, and despite being less potent than CBDCA, AP5280 produced less systemic toxicity relative to its antitumor activity and thus has a greater therapeutic index. On the basis of the improved therapeutic index evidenced in these models, AP5280 has been advanced into clin. trials.

Answer 16:

Bibliographic Information

Low Dose Carboplatin Combined With Angiostatic Agents Prevents Metastasis in Human Testicular Germ Cell Tumor Xenografts. Abraham, Dietmar; Abri, Samad; Hofmann, Michael; Hoeltl, Wolfgang; Aharinejad, Seyedhossein. Laboratory for Cardiovascular Research, Department of Anatomy, University of Vienna, Vienna, Austria. Journal of Urology (Hagerstown, MD, United States) (2003), 170(4, Pt. 1), 1388-1393. Publisher: Lippincott Williams & Wilkins, CODEN: JOURAA ISSN: 0022-5347. Journal written in English. CAN 140:156885 AN 2003:897212 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Low dose chemotherapy combined with angiogenesis inhibitors has been shown to be more effective for exptl. tumor treatment than chemotherapy alone. To our knowledge whether germ cell tumors could benefit from this treatment strategy remains to be evaluated. We examd. the efficacy of angiostatic thrombospondin-1 (TSP-1), endostatin and combined angiostatic/low dose carboplatin in mice xenografted with human nonseminomatous germ cell tumor. chain reaction. We monitored tumor progression and angiogenesis in the established model of human nonseminomatous germ cell tumor xenograft in 120 SCID mice using intravital video microscopy, immunocytochem. and real-time polymerase. Mice received TSP-1 (20 mg/kg daily) or endostatin (10 mg/kg daily) s.c. (via osmotic mini pumps) for 2 wk starting 15 days after cancer cell grafting, carboplatin cycled twice (30 mg/kg i.p. days 14 and 21 after cancer cell grafting), or a combination of carboplatin with TSP-1 or endostatin. Untreated, sham and tumor bearing mice treated

with Ringer's soln. served as controls. RESULTS: Primary tumor development was not affected in mice treated with TSP-1, endostatin or carboplatin alone. All animals had metastases at 6 mo, while metastasis did not develop following the combination of carboplatin with TSP-1 or endostatin. This combined therapy suppressed tumor angiogenesis, enhanced apoptosis in tumor cells and decreased vascular endothelial growth factor-A tissue mRNA expression vs. controls ($p < 0.05$). These data indicate that angiostatic agents added to low dose carboplatin have the ability to suppress the progression of human germ cell tumor xenografts toward a metastatic phenotype. Therefore, this treatment strategy might be beneficial to prevent metastasis in germ cell tumors.

Answer 17:

Bibliographic Information

Studies with CWR22 xenografts in nude mice suggest that ZD1839 may have a role in the treatment of both androgen-dependent and androgen-independent human prostate cancer. Sirotnak, Francis M.; She, Yohung; Lee, Fei; Chen, Jing; Scher, Howard I. Program in Molecular Pharmacology and Therapeutics and Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. Clinical Cancer Research (2002), 8(12), 3870-3876. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 139:143462 AN 2002:974069 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

These studies examd. the effect of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor ZD1839 (Iressa) on CWR22 prostate tumors in nude mice. The effect of ZD1839 was also examd. in combination with either bicalutamide (Casodex) or cytotoxic agents against a hormone-dependent or -independent variant of CWR22, resp. The xenografts were grown for 4-7 days, then tumor measurements were made and therapy initiated. ZD1839 and bicalutamide were given p.o. on a once-daily, 5-day schedule for 2 successive weeks. Carboplatin and paclitaxel were given every 3-4 days for a total of four doses. Measurements of tumor vol. were made twice weekly during treatment and for 2 wk after treatment. The effect of ZD1839 on EGFR function was assessed by Western blotting of EGFR and its phosphorylated form in CWR22 and variant tumors before and after treatment with this agent. ZD1839 at its max. tolerated dose (150 mg/kg) inhibited the growth of androgen-dependent CWR22 by 54%, and the growth of two variants with different degrees of androgen independence and androgen receptor gene expression (CWR22LD1 and CWR22RV1) by 76%. The effects of ZD1839 were similar to those recorded for phosphorylation of EGFR as detd. by Western blotting. Co-administration of ZD1839 at its max. tolerated dose markedly increased the antiproliferative action of the antiandrogen bicalutamide against CWR22LD1. In fact, combining ZD1839 with a suboptimal dose of bicalutamide was more effective than a higher dose of bicalutamide alone. Co-administration of ZD1839, which required a 2-3-fold attenuation of dose to avoid toxicity, also markedly increased the therapeutic activity of carboplatin and paclitaxel against CWR22RV1, bringing about regression to a degree not seen with either agent alone. Tumor-free mice were seen only with the combination of ZD1839 and paclitaxel.

The results obtained in these related and highly relevant models of human prostate cancer suggest that ZD1839 may have a role in enhancing existing treatments of androgen-dependent and -independent forms of this disease in patients.

Answer 18:

Bibliographic Information

Antiangiogenic and Antitumor Effects of a Protein Kinase Cβ Inhibitor in Human Breast Cancer and Ovarian Cancer Xenografts. Teicher, Beverly A.; Menon, Krishna; Alvarez, Enrique; Shih, Chuan; Faul, Margaret M. Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, USA. Investigational New Drugs (2002), 20(3), 241-251. Publisher: Kluwer Academic Publishers, CODEN: INNDDK ISSN: 0167-6997. Journal written in English. CAN 138:247991 AN 2002:512394 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In cell culture, the compd. 317615·2HCl, a potent inhibitor of VEGF-stimulated HUVEC proliferation, was not very effective against MX-1 breast cancer cells (IC50 = 8.1 μM) or SKOV-3 ovarian carcinoma cells (IC50 = 9.5 μM). Exposure to combinations of paclitaxel

or carboplatin and 317615·2HCl with MX-1 cells in culture resulted in cell survival that reflected primarily additivity of the 2 agents. Exposure of SKOV-3 cells to paclitaxel or carboplatin along with 317615·2HCl resulted in cell survivals that reflected additivity of 317615·2HCl with paclitaxel and greater-than-additive cytotoxicity with carboplatin. Administration of 317615·2HCl orally twice daily to nude mice bearing s.c. MX-1 tumors or SKOV-3 tumors resulted in a decreased no. of intratumoral vessels as detd. by CD31 and CD105 staining with decreases of 35% and 43% in MX-1 tumors and 60% and 75% in SKOV-3 tumors, resp. 317615·2HCl was an active antitumor agent against the MX-1 xenograft and increased the tumor growth delay produced by paclitaxel by 1.7-fold and the tumor growth delay produced by carboplatin by 3.8-fold. Administration of 317615·2HCl also increased the tumor growth delay produced by fractionated radiation therapy in the MX-1 tumor. Treatment with 317615·2HCl alone increased the lifespan of animals bearing i.p. SKOV-3 xenografts by 1.9 fold compared with untreated control animals. The combination of paclitaxel and 317615·2HCl resulted in 100% 120-day survival of SKOV-3 bearing animals. Administration of 317615·2HCl along with carboplatin to animals bearing the SKOV-3 tumor produced a 1.8-fold increase in lifespan compared with carboplatin alone. 317615·2HCl is a promising new antiangiogenic agent that is in early phase clin. testing.

Answer 19:

Bibliographic Information

BNP7787, a novel protector against platinum-related toxicities, does not affect the efficacy of cisplatin or carboplatin in human tumor xenografts. Boven, E.; Verschraagen, M.; Hulscher, T. M.; Erkelens, C. A. M.; Hausheer, F. H.; Pinedo, H. M.; van der Vijgh, W. J. F. Department of Medical Oncology, Vrije Universiteit Medical Centre, Amsterdam, Neth. European Journal of Cancer (2002), 38(8), 1148-1156. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 138:163038 AN 2002:339566 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BNP7787 (2',2'-dithio-bis-ethane sulfonate sodium), a water-sol. disulfide, is chem. and mechanistically different from other sulfur-contg. chemoprotective agents. Presently, BNP7787 is under investigation for its protective properties with regard to the side-effects of platinum compds. In this study, we evaluated BNP7787, Mesna and amifostine for their effects on the antitumor activity of platinum compds. Continuous exposure to BNP7787 did not affect the antiproliferative effects of cisplatin or carboplatin, but the efficacy of both compds. was reduced in the presence of Mesna in vitro in two human ovarian cancer cell lines. BNP7787 or amifostine combined with cisplatin or carboplatin given in std. schedules for the treatment of nude mice bearing well-established OVCAR-3 xenografts did not interfere with platinum-induced inhibition of tumor growth. Of interest, BNP7787 or amifostine co-administered with carboplatin was significantly more effective than carboplatin alone ($P<0.01$). In the presence of amifostine, doses of cisplatin and carboplatin could be safely increased by factors of 1.6 and 1.5, resp. Unlike in a previous study of BNP7787 in tumor-bearing rats, BNP7787 did not protect against addnl. wt. loss following treatment with higher doses of cisplatin in OVCAR-3-bearing mice. Pharmacokinetics of (mixed) disulfides including BNP7787 and extractable Mesna in deproteinized plasma revealed a rapid disappearance of BNP7787 and an AUC5-60 value of Mesna 9-fold lower than that calcd. after an equiv. dose of Mesna by wt. We can conclude that BNP7787 does not interfere with the antitumor activity of platinum compds. in vitro and in vivo. Clin. trials are underway to evaluate the protection of normal tissues by BNP7787 when combined with cisplatin.

Answer 20:

Bibliographic Information

Efficient carboplatin single therapy in a mouse model of human testicular nonseminomatous germ cell tumor. Aharinejad, Seyedhossein; Fink, Melanie; Abri, Hojatollah; Nedwed, Stephan; Schlag, Michael G.; MacFelda, Karin; Abraham, Dietmar; Miksovsky, Aurelia; Holtl, Eva; Holtl, Wolfgang. Laboratory for Cardiovascular Research, Department of Anatomy, Center for Biomedical Research, University of Vienna, Vienna, Austria. Journal of Urology (Hagerstown, MD, United States) (2002), 167(1), 368-374. Publisher: Lippincott Williams & Wilkins, CODEN: JOURAA ISSN: 0022-5347. Journal written in English. CAN 137:119162 AN 2002:37948 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To decrease morbidity of cisplatin-based combination therapy, carboplatin vs. etoposide single therapy was examd. in an animal model. SCID mice bearing testicular nonseminomatous germ cell tumor xenografts received 120 mg carboplatin/kg as a single cycle, 60 or 30 mg carboplatin/kg cycled twice, 80, 50 or 30 mg etoposide/kg cycled twice, or Ringer's soln. Histol. and immunocytochem. testing, in vivo microscopy, vascular corrosion casting, serum tumor markers, complete blood count and real-time polymerase chain reaction were used to monitor therapy efficacy. Carboplatin at 60 mg/kg cycled twice eradicated the tumor and reduced vascular d. and vascular endothelial growth factor-A mRNA. Elevated tumor markers returned to basal values after carboplatin administration. Therapy was well tolerated; thrombocytopenia had disappeared 6 wk after therapy and the animals were tumor-free 6 mo after treatment. Although 120 mg carboplatin/kg eradicated the tumor, it resulted in extensive mortality and morbidity. Single treatment with 30, 50 and 80 mg etoposide/kg failed. Carboplatin single therapy was highly effective in this nonseminomatous germ cell tumor model and it may be useful in future clin. trials in patients with high-risk stage I nonseminomatous germ cell cancer for reducing morbidity from cisplatin-based combination therapy. Vascular d. and vascular endothelial growth factor mRNA were elevated in this animal model and deserve further study as potential risk factors in nonseminomatous germ cell tumor cases.

Answer 21:

Bibliographic Information

Effects of mitomycin C and carboplatin pretreatment on multidrug resistance-associated P-glycoprotein expression and on subsequent suppression of tumor growth by doxorubicin and paclitaxel in human metastatic breast cancer-xenografted nude mice. Ihnat, Michael A.; Nervi, Angela M.; Anthony, Stephen P.; Kaltreider, Ronald C.; Warren, Amy J.; Pesce, Carrie A.; Davis, Stacey A.; Lariviere, Jean P.; Hamilton, Joshua W. Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH, USA. Oncology Research (1999), 11(7), 303-310. Publisher: Cognizant Communication Corp., CODEN: ONREE8 ISSN: 0965-0407. Journal written in English. CAN 133:344264 AN 2000:517393 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Mitomycin C and carboplatin each suppressed cell P-glycoprotein levels in human MDA-MB-435 cells xenografted as solid tumors into the lateral mammary fat pads of female nude mice, with a similar time course as had previously been obsd. in cell culture. Pretreatment of the mice with mitomycin C or carboplatin 48-72 h prior to receiving either doxorubicin or paclitaxel caused a greater redn. of tumor growth rate than did either of the latter agents alone or given simultaneously. These data suggest that a combination chemotherapy regimen consisting of a DNA crosslinking agent given to modulate the multidrug-resistant phenotype, followed by a 2nd cytotoxic agent, may be an effective treatment for human patients with de novo or late-stage-acquired multidrug-resistant malignancies.

Answer 22:

Bibliographic Information

Development of an orally active platinum anticancer drug: JM216. Barnard, C. F. J.; Raynaud, F. I.; Kelland, L. R. Johnson Matthey Technology Centre, Blount's Court, Sonning Common, Reading, UK. Topics in Biological Inorganic Chemistry (1999), 1(Metallopharmaceuticals I), 45-71. Publisher: Springer-Verlag, CODEN: TBICFV Journal; General Review written in English. CAN 132:116943 AN 1999:605854 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review with 54 refs. Following the successful introduction of the less toxic analog of cisplatin, carboplatin, into clin. practice in the early 1980s, a collaborative program of research was established between Johnson Matthey, the Institute of Cancer Research and Bristol Myers Squibb. Its aim was to discover and develop an orally active platinum drug possessing at least comparable antitumor activity to that of cisplatin but a toxicol. profile reminiscent of carboplatin. A new class of platinum compds. synthesized specifically to circumvent the poor gastrointestinal absorption of cisplatin and carboplatin possessed the properties of having a relatively low mol. wt., were lipophilic, neutral, kinetically inert and acid stable. The resulting lead compd. JM216 (bis-acetato-ammine

dichlorocyclohexylamine platinum IV), an example of the Pt(IV) mixed ammine/amine dicarboxylate dichloride series, entered clin. trials at the Royal Marsden Hospital, London, in 1992. Preclinically, JM216 was demonstrated to possess oral antitumor activity in mice bearing the ADJ/PC6 plasmacytoma and a panel of human ovarian carcinoma xenografts broadly equiv. to that obsd. for i.v. administered cisplatin or carboplatin. Oral antitumor activity was greater when using a daily×5 split dose schedule vs. weekly dosing, probably as a result of saturable oral absorption. In vitro against panels of cisplatin-sensitive and -resistant human tumor cell lines, JM216 exhibited a similar potency to that of cisplatin and was able to circumvent acquired cisplatin resistance due to reduced drug transport. The drug's toxicol. profile in rodents was similar to that of carboplatin with myelosuppression being dose-limiting with no obvious nephro- or neurotoxicity. The metab. of JM216 is complex with up to six metabolites being formed; the major metabolite in man being cis-ammine dichloro(cyclohexylamine) platinum (II) (JM118). Glutathione conjugation represents a major deactivation pathway for JM216. The initial single dose phase I clin.
trial was incapable of defining a max. tolerated dose (MTD) due to absorption-limited non-linear pharmacokinetics. A second phase I trial daily for 5 days, showed dose-limiting toxicities of thrombocytopenia and neutropenia. Recommended phase II doses were 100 and 120 mg/m2/day×5 for previously treated and untreated patients, resp. Phase II trials are currently ongoing in a no. of tumor types including prostate, ovarian and lung.

Answer 23:

Bibliographic Information

Antitumor effect of CPT-11, a camptothecin derivative, on human testicular tumor xenografts in nude mice. Miki, Tsuneharu; Sawada, Masumi; Nonomura, Norio; Kojima, Yasuyuki; Okuyama, Akihiko; Maeda, Osamu; Saiki, Shigeru; Kotake, Toshihiko. Department of Urology, Osaka University Medical School, Osaka, Japan. European Urology (1997), 31(1), 92-96. Publisher: S. Karger AG, CODEN: EUURAV ISSN: 0302-2838. Journal written in English. CAN 129:285665 AN 1998:542001 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor effect of CPT-11, a camptothecin deriv., on two human testicular embryonal carcinomas (TTSC-2 and TTSC-3) heterotransplanted into nude mice was studied. Tumor-bearing nude mice were given daily i.p. injections of the anticancer drugs in 0.1 mL saline 3 times at 3-day intervals. At the end of the expts. tumors were resected and subjected to light-microscopic observation. When 10, 30 and 50 mg/kg of CPT-11 was administered to tumor-bearing mice i.p., the antitumor effect of CPT-11 was obsd. dose-dependently in both TTSC-2 and TTSC-3. When 30 mg/kg of CPT-11 was administered in combination with CDDP, complete tumor regression was obsd. in both TTSC-2 and TTSC-3 tumors. Histol. findings correlated well with the decrease in tumor vol. of treated tumors. No mice died after treatment with CPT-11 in a single-agent and combination chemotherapy. Chemotherapy with CPT-11 was an effective and safe method against human testicular tumors heterotransplanted in nude mice.

Answer 24:

Bibliographic Information

Encapsulation of the transition metal compounds carboplatin (CP) and lobaplatin (LP) in different types of liposomes and their physicochemical, biochemical and biological characterization. Reszka, Regina; Fichtner, Iduna; Goan, Silvia-Renate; Rudolph, Michael; Winter, Roland. Max-Delbruck-Centrum fur Molekulare Medizin, Berlin, Germany. Editor(s): Trautwein, Alfred X. Bioinorganic Chemistry (1997), 145-166. Publisher: Wiley-VCH Verlag GmbH, Weinheim, Germany CODEN: 65TRAJ Conference written in English. CAN 128:248493 AN 1998:231297 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The dose limiting factor in the treatment of head and neck as well as ovarian cancer with carboplatin and more recently lobaplatin is the myelotoxicity of both substances. In contrast, a stimulation of hematopoiesis was obsd. when these anticancer agents were applied to mice or rats in a specific liposomally encapsulated form. The mechanism of this hematopoietic stimulation, the therapeutic efficacy and the alteration of the pharmacokinetic behavior were investigated with respect to the lipid compn., the prepn. technique, the size of

the liposomes, and the interaction between the platinum compds. and the liposomal components. In vitro expts. were carried out to investigate the role of peritoneal macrophages in the decompn. of encapsulated carboplatin and the stimulation of cytokine release as a possible main step for the activation of the hematopoietic system. During the biophys. studies, we were not able to detect a significant perturbation or intermol. interactions of carboplatin or lobaplatin with the lipid system (1,2 Dipalmitoyl-sn-glycero-3-phosphocholine, DPPC). The in vitro treatment of peritoneal macrophages (mice) with carboplatin or lobaplatin encapsulated in reverse phase evapn. vesicles (REV, HEPC:CH, molar ratio 1:0.25 or 1:0.1, size distribution 0.2 to 1.5 μm) showed a stimulation of cytokines measured for instance as TNF-release. In parallel no decompn. products of carboplatin could be detected by HPLC. Following a single (i.v. or i.p.) injection, carboplatin liposomes (CPL) induced a five- or tenfold, at least 4 mo lasting increase in peripheral white blood cells compared to the free drug in mice. A second administration in a 7-10 wk distance was able to a repeated stimulation. The colony forming activity and the percentage of cells in S-phase were elevated in spleen three days after treatment of mice with CPL, while these parameters remained unchanged in the bone marrow.
Serum taken from CPL-treated nude or normal mice induced a significant colony formation of bone marrow cells in a soft agar culture. In the syngeneic ascitic murine P388 leukemia and the MethA sarcoma liposomal encapsulation resulted in a loss of antitumor activity. On contrary, in 3/6 solidly growing breast carcinomas, xenografted to nude mice, CPL had a superior tumor inhibiting effect compared to free carboplatin, which could be further improved by using the combination of free and liposomal drug. A combination of CPL with either cyclophosphamide or free carboplatin increased the antitumor activity and prevented the cytostatic-induced leukopenia. As mechanism for this unexpected pharmacol. behavior of liposomal carboplatin, we suggested, that the vesicles are taken up by the monocyte/macrophage system as their natural target. Within these cells CPL are metabolized and induce the prodn. and release of cytokines which, secondarily, stimulate hematopoiesis. Pharmacokinetic data and measurements of cytokine levels in serum of treated mice support this hypothesis. Free carboplatin, empty liposomes or cisplatin-liposomes never caused a similar pharmacol. behavior. Lobaplatin encapsulated in REV (HEPC:CH, molar ratio 1:0.1, size distribution 0.2 to 1.5 μm) will be tested further on in vivo. First preliminary observations suggest that LPL can also stimulate the hematopoietic system.

Answer 25:

Bibliographic Information

Continuous cell lines derived from head and neck tumors for mechanistic studies in vitro and in a nude mouse animal model. Knebel, J. W.; Eckardt, A.; Fokas, K.; Aufderheide, M.; Nolte, M. Institute of Experimental Pathology, Hannover Medical School, Hannover, Germany. International Congress Series (1996), 1114(Head and Neck Cancer: Advances in Basic Research), 111-119. Publisher: Elsevier, CODEN: EXMDA4 ISSN: 0531-5131. Journal written in English. CAN 126:54594 AN 1997:37414 CAPLUS

Abstract

In a series of expts. the authors established and characterized continuous cell lines of different squamous cell carcinomas. The isolated cells grew in epithelial clusters and expressed cytokeratin. Their differentiation pattern and capacity differ to a certain extent. Using these in vitro systems the authors studied the effects of different chemotherapeutic drugs (e.g., MTX, 5-FU, CBDCA and Taxol). Injection of HN SCC-001 cells into nude mice gave rise to serially transplantable s.c. tumors. The cell line as well as the xenotransplants showed the phenotype and genotype characteristics of the primary tumor.

Answer 26:

Bibliographic Information

Amifostine (Ethyol): pharmacokinetic and pharmacodynamic effects in vivo. Van Der Vijgh, W. J. F.; Korst, A. E. C. Department of Medical Oncology, University Hospital Vrije Universiteit, Amsterdam, Neth. European Journal of Cancer, Part A (1996), 32A(Suppl. 4), S26-S30. Publisher: Elsevier, CODEN: EJCTEA Journal; General Review written in English. CAN 126:54355 AN 1997:28350 CAPLUS

Abstract

A review with 21 refs. Amifostine administered to cancer patients is rapidly cleared from plasma by a biphasic decay with an alpha half-life (T1/2α) of 0.88 min and a T1/2β of 8.8 min. The result is that more than 90% of the drug has disappeared from the plasma compartment 6 min after i.v. (i.v.) administration. Only approx. 1% of the dose appears in the ascites. Animal studies indicate that amifostine is primarily excreted in urine-approx. 6% of the dose is excreted in the urine as amifostine and its metabolites WR-1065 and disulfides-which means that a large percentage of the dose is taken up by the tissues. Maximal tissue concns. of WR-1065 and the disulfides were obtained between 10 and 30 min after an i.p. injection of amifostine in mice, with the lowest concns. in tumor tissues. Because WR-1065 gives protection to normal tissues rather than rescue, the pharmacokinetic data indicate that amifostine must be given shortly before administration of the cytostatic drug or radiation from which protection is required. For these reasons, amifostine is given to patients as a 15-min i.v. infusion before cisplatin and carboplatin to protect against their dose-limiting toxicities. In some regimens carboplatin is combined with three doses of amifostine because of the high concn. of the active carboplatin species during the first 4 h after administration. When carboplatin was administered as a 15-min i.v. infusion of 400 mg/m2 and amifostine as a 15-min i.v. infusion of 740 mg/m2 just before and 2 and 4 h after carboplatin, the area under the plasma concn.-time curve for ultrafilterable platinum increased from 253 ± 45 μM.h (n = 6) for carboplatin alone to 305 ± 63 μM.h (n = 11) for carboplatin + three doses of amifostine. Expts. in nude mice bearing OVCAR-3 xenografts showed that amifostine, given once before cisplatin or three times in combination with carboplatin, did not affect the antitumor effect of these drugs.

When amifostine was only given just before carboplatin, it even stimulated the antitumor effect of carboplatin significantly.

Answer 27:

Bibliographic Information

Sensitization by interleukin-1α of carboplatinum anti-tumor activity against human ovarian (NIH:OVCAR-3) carcinoma cells in vitro and in vivo. Wang, Zheng; Lee, Kang Bo; Reed, Eddie; Sinha, Birandra K. Clinical Pharmacology Branch, National Cancer Institute, National Institutes Health, Bethesda, MD, USA. International Journal of Cancer (1996), 68(5), 583-587. Publisher: Wiley-Liss, CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 126:42370 AN 1997:2572 CAPLUS

Abstract

Cytokines are directly cytotoxic to tumor cells in vitro and in vivo, and interleukin-1α (IL-1α) potentiates the cytotoxicity of a no. of clin. active drugs in several human tumor cells, including carcinomas of the breast and ovary. In this study, the authors found that IL-1α potentiated the cytotoxicity of carboplatin in human ovarian NIH:OVCAR-3 cancer cells during simultaneous drug exposure in vitro. Human ovarian carcinoma NIH:OVCAR-3 cells are resistant to clin. relevant concns. of chemotherapeutic agents, including cisplatin. Both carboplatin and IL-1α as single agents inhibited the growth of NIH:OVCAR-3 cells grown as xenograft in nude mice; however, carboplatin was more effective in delaying tumor growth, and this inhibition was dose-dependent. Treatment with IL-1α followed by carboplatin caused a significant delay in tumor growth, resulting in a significant enhancement (4-fold) of the anti-tumor effect of carboplatin. In vitro potentiation of carboplatin cytotoxicity by IL-1α did not involve formation of nitric oxide as IL-1 or combinations of IL-1 with carboplatin failed to modulate basal nitric oxide prodn. in OVCAR-3 cells. Potentiation of the anti-tumor activity of carboplatin by IL-1α was due to a significant (3- to 4-fold) increase in the accumulation of total Pt in IL-1-treated tumor xenograft, resulting in a 2-fold increase in DNA-Pt adduct formation in these tumors. In contrast, IL-1 had no significant effect on DNA-Pt adduct formation in the kidney. The potent synergy of IL-1α and carboplatin in vitro and in vivo against ovarian carcinoma cells suggests that combinations of carboplatinum and interleukin-1α may be effective against this disease in the clinic.

Answer 28:

Bibliographic Information

Antagonistic effect of amphotericin B on carboplatin antitumor activity in human osteosarcoma xenografts. Crnalic, Sead; Bergstroem, Per; Loefvenberg, Richard; Henriksson, Roger; Brostroem, Lars-Aake. Dep. Orthopaedics Oncol., Umea Univ. Hosp., Umea, Swed. Anti-Cancer Drugs (1996), 7(4), 489-492. Publisher: Rapid Science Publishers, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 125:158060 AN 1996:471911 CAPLUS

Abstract

Amphotericin B (AmB), a polyene antifungal antibiotic, has been shown to potentiate the cytotoxic effect of different chemotherapeutic drugs in vivo and in vitro. The purpose of this study was to det. whether AmB could enhance the carboplatin antitumor activity in a human osteosarcoma xenograft model. Nude mice, bearing s.c. transplanted osteosarcoma xenografts, received i.p. an injection of AmB (5 mg/kg) 6 h prior to carboplatin (20 mg/kg) or each of the drugs sep. The effect of treatment was assessed by analyzing tumor growth delay and T/C ratio. Carboplatin clearly reduced tumor growth when administered alone. However, an unexpected interaction was seen where AmB significantly decreased the antitumor effect of carboplatin. The present results contradict some earlier in vitro studies and indicate the complexity of this interaction in vivo. Hence, it seems that interactive phenomena in one exptl. model, and esp. with regard to AmB, cannot be universally applied to all exptl. situations.

Answer 29:

Bibliographic Information

Interaction between amphotericin B, carboplatin, and radiation in human osteosarcoma xenografts in nude mice. Crnalic, Sead; Bergstroem, Per; Loefvenberg, Richard; Henriksson, Roger; Brostroem, Lars-Aake. Department Orthopaedics, Umea University Hospital, Umea, Swed. Oncology Reports (1996), 3(4), 609-612. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 125:104313 AN 1996:438415 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In order to evaluate and modify the radiosensitizing effect of carboplatin, amphotericin B (AmB) was given as pretreatment to nude mice with bilateral s.c. human osteosarcoma xenografts. One of the 2 tumors in each animal was irradiated with a single x-ray dose of 12 Gy following treatment with AmB (5 mg/kg), or carboplatin (20 mg/kg), or AmB (5 mg/kg) plus carboplatin (20 mg/kg). Compared with nontreated tumors, a redn. of tumor growth was obsd. after irradn. Carboplatin in itself reduced tumor growth and also added to the effect of radiation. An unexpected interaction was seen where AmB decreased the effect of either carboplatin or radiation alone or the two given concomitantly. The results are contradictory to those of some earlier in vitro studies and imply that the interactive effect in general and esp. with regard to AmB cannot be universally applied to all exptl. situations.

Answer 30:

Bibliographic Information

Potentiation of antitumor activities of carboplatin and camptothecin by interleukin-1α against human ovarian carcinoma in vivo. Wang, Zheng; Benchekroun, M. Nabil; Sinha, Birandra K. Biochemical Molecular Pharmacology Section, National Cancer Institute, Bethesda, MD, USA. Anticancer Research (1994), 14(5A), 1723-6. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 122:281602 AN 1995:534222 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Interleukin-1α significantly potentiated the cytotoxicity of carboplatin (8-fold) and camptothecin (4-fold) during simultaneous drug exposure in human ovarian NIH: OVCAR-3 cancer cells in vitro. Treatment of human ovarian tumor cells grown as xenografts in nude mice with IL-1α followed by either carboplatin or CTP-11 at minimally toxic doses significantly (2-3-fold and 7-fold for carboplatin and CTP-11, resp.) enhanced antitumor activity of either agent alone, indicating that IL-1α-drug combinations may be potentially more effective for the treatment of ovarian tumors, including those difficult to cure in the clinic.

Answer 31:

Bibliographic Information

Pharmacological effects of carboplatin-liposomes (CPL) in mice: a review of present knowledge. Fichtner, Iduna; Reszka, Regina; Goan, Silvia R.; Naundorf, Helga; Hentschel, Michael. Max-Delbrueck-Center of Molecular Medicine, Berlin, Germany. Journal of Liposome Research (1995), 5(1), 75-89. CODEN: JLREE7 ISSN: 0898-2104. Journal; General Review written in English. CAN 122:229898 AN 1995:475444 CAPLUS

Abstract

A review with 12 refs. Carboplatin was encapsulated in reverse phase evapn. vesicles (REV) consisting of hydrogenated egg phosphatidylcholine and cholesterol (HEPC:CH) in a molar ratio of 1 : 0.25. Both antitumor effects, influence on hematopoiesis and cytokine levels were measured in mice after i.p. or i.v. injection in comparison to the free drug. In the syngeneic murine P 388 leukemia and the Meth A sarcoma liposomal encapsulation resulted in a loss of antitumor activity. On contrary, in 3/6 breast carcinomas xenografted to nude mice CPL had a superior tumor inhibiting effect compared to free carboplatin, which could be further improved by using the combination of free and liposomal drug. As reported earlier CPL induced a five- or tenfold, at least 30 days lasting increase in peripheral white blood cells after only one single i.v. or i.p. injection, resp. A second administration in a 7-10 wk distance was able to a repeated stimulation. The colony forming activity and the percentage of cells in S-phase were elevated in spleen cells three days after treatment of mice with CPL while these parameters remained unchanged in the bone marrow. Serum taken from CPL-treated nude or normal mice induced significantly colony formation of bone marrow cells in a soft agar culture. Concerning side effects, CPL led to a 15 days lasting blockade of RES (measured by carbon clearance), to a 7 days lasting increase of serum glutamate oxalacetate transaminase and a diminution of body wt. while the blood urea levels as parameter of kidney toxicity were in normal range. A combination of CPL with either cyclophosphamide or free carboplatin prevented the cytostatic-induced leukopenia.

Answer 32:

Bibliographic Information

Effects of the modulating agent WR2721 on myelotoxicity and antitumor activity in carboplatin-treated mice. Treskes, Marco; Boven, Epie; van de Loosdrecht, Arjan A.; Wijffels, Josien F. A. M.; Cloos, Jacqueline; Peters, Godefridus J.; Pinedo, Herbert M.; van der Vijgh, W. J. F. Dep. Oncol., Free Univ. Hosp., Amsterdam, Neth. Eur. J. Cancer, Part A (1994), 30A(2), 183-7. CODEN: EJCTEA Journal written in English. CAN 121:73176 AN 1994:473176 CAPLUS

Abstract

The selective modulation of carboplatin [diammine(1,1-cyclobutanedicarboxylato)platinum(II)]-induced myelotoxicity was investigated in mice, using the protective agent WR2721 [S-2-(3-aminopropylamino)ethylphosphorothioic acid, ethiofos]. In female BALB/c mice, WR2721 (200 mg/kg i.p., i.p.) partly prevented the redn. of in vitro proliferation of whole bone marrow cells and non-adherent cells when administered at different time points relative to 90 mg/kg carboplatin (i.p.). Protection was highest when WR2721 was administered 5 min prior to carboplatin. In vitro proliferation of whole bone marrow cells and non-adherent cells in liq. culture increased from 15% of control for carboplatin alone to 45% when WR2721 was administered 5 min prior to carboplatin. However, WR2721 did not significantly prevent the loss in clonogenic capacity of early hematopoietic progenitors in the bone marrow, as detd. by a bilayered soft agar colony forming units assay. In nude mice, bearing well-established s.c. human ovarian carcinoma xenografts OVCAR-3, WR2721 (200 mg/kg i.p.) 5 min prior to i.v. carboplatin allowed a 1.5-fold increase in the max. tolerated dose of carboplatin as detd. by overall wt. loss. WR2721 alone did not affect tumor growth. However, WR2721 had a potentiating effect on the tumor growth inhibition of a std. dose of carboplatin in this model. Minimal tumor vol. compared to control (T/C) decreased from 9.4% with carboplatin alone to 2.2% with WR2721 5 min prior to the same dose of carboplatin. Specific growth delay (SGD) increased from 7.4 to 10.3. With the 1.5-fold increased, equitoxic dose of carboplatin in combination with WR2721, the antitumor activity was only slightly further increased (T/C = 1.4%, SGD = 10.5).

Answer 33:

Bibliographic Information

Comparative study of antitumor agents in serum and tumor between nude mouse and human. Inoue, So. Sch. Med., Keio Univ., Tokyo, Japan. Keio Igaku (1991), 68(1), 57-65. CODEN: KEIGAS ISSN: 0368-5179. Journal written in Japanese. CAN 115:188 AN 1991:400188 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The pharmacokinetic comparison between nude mouse and human beings is important to using the human tumor xenograft-nude mouse system as a screening panel for newly developed antitumor agents. Mitomycin C, adriamycin, 5-fluorouracil, cisplatin, and the platinum-related compds. (carboplatin and DWA2114R) were administered to nude mice bearing human tumor xenografts in max. tolerated doses and to patients with cancer in conventionally available doses in clinics. The concns. of antitumor agents in serum and tumor were detected by bioassay, HPLC, and the at. absorption method. The max. serum concn. (Cmax) in μg/mL and concn. in tumor (T) in μg/g in nude mouse and human were compared to each other and the shift of drugs from serum to tumor was calcd. as T/Cmax. Although the different doses of the agents were administered in nude mice and humans, the T/Cmax ratios were similar to each other.

Answer 34:

Bibliographic Information

Comparative antitumor activity of cisplatin and two new cisplatin-analogs JM8 and JM9 in human testicular carcinoma xenografts. Harstrick, A.; Casper, J.; Schmoll. H. J. Abt. Haematol. Onkol., Med. Hochsch. Hannover, Hannover, Fed. Rep. Ger. International Journal of Andrology (1987), 10(1), 139-45. CODEN: IJANDP ISSN: 0105-6263. Journal written in English. CAN 107:70346 AN 1987:470346 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The comparative antitumor activity of cisplatin, JM8 and JM9 was tested using a panel of different heterotransplanted human testicular tumor cell lines. All drugs were applied at equitoxic doses in a 5 day schedule. In the two cisplatin sensitive cell lines 2102 EP and H 12.1 both analogs were inferior to cisplatin. No significant therapeutic effect was achieved with any of the three drugs in the cisplatin resistant line H 23.1. Thus JM8 and JM9 seem to be less active in cisplatin sensitive tumors and seem to be of no advantage in the case of cisplatin resistance.

Answer 35:

Bibliographic Information

Cytotoxicity of cisplatin and cisdiammine-1,1-cyclobutane dicarboxylate in MGH-U1 cells grown as monolayers, spheroids, and xenografts. Erlichman, Charles; Vidgen, Danka; Wu, Anna. Ontario Cancer Inst., Univ. Toronto, Toronto, ON, Can. JNCI, Journal of the National Cancer Institute (1985), 75(3), 499-505. CODEN: JJIND8 ISSN: 0198-0157. Journal written in English. CAN 103:153566 AN 1985:553566 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The cytotoxicity of cisplatin [15663-27-1] and cis-diammine-1,1-cyclobutanedicarboxylate (CBDCA) [41575-94-4] was examd. using the MGH-U1 human bladder carcinoma cell line, grown as monolayer cultures, multicellular tumor spheroid(s) (MTS), and xenografts in immune-deprived CBA/CaJ mice. The cell survival of exponentially growing monolayers and MTS treated with cisplatin declined in a monoexponential fashion with a concn. of drug resulting in 10% colony survival (D10) of 7.75 μg/mL and 9.5 μg/mL, resp. MTS growth delay detn. demonstrated a drug concn.-dependent increase in growth delay and a correlation between decreasing surviving fraction and increasing growth delay. In vivo treatment of MGH-U1 xenografts with cisplatin caused a modest decrease in surviving fraction although the xenografted cells treated in vivo demonstrated the same sensitivity to cisplatin as those cells maintained continuously in vitro. The D10 for CBDCA treatment was 246 μg/mL for exponentially growing monolayer cells and 196 μg/mL for MTS. Growth-delay

studies with CBDCA showed a concn.-dependent increase in spheroid growth delay and a correlation between decreasing surviving fraction and growth-delay similar to those with cisplatin. The conclusions were that: 1) cisplatin and CBDCA do not have any difficulty penetrating into spheroids, 2) both agents appear to be active against the noncycling poorly nourished cells found near the necrotic center of spheroids 3) both cisplatin and CBDCA are cytotoxic toward MGH-U1 cells but cisplatin is .apprx.20-30 times more effective, and 4) the limited cytotoxic effect of cisplatin in vivo may be due to the low area under the concn.-time curve achieved in vivo and not due to intrinsic cell resistance.

Answer 36:

Bibliographic Information

Cell survival in four ovarian carcinoma xenografts following in vitro exposure to melphalan, cisplatin and cis-diammine-1,1-cyclobutanedicarboxylateplatinum(II) (CBDCA, JM8). Jones, Adrian C.; Wilson, Patricia A.; Steel, G. Gordon. Radiother. Res. Unit, Inst. Cancer Res., Sutton, UK. Cancer Chemotherapy and Pharmacology (1984), 13(2), 109-13. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 101:183580 AN 1984:583580 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Four human ovarian carcinoma xenografts were established and maintained in immune-suppressed mice. Cells obtained from these xenografts were exposed in vitro to melphalan [148-82-3], JM8 [41575-94-4], and cisplatin [15663-27-1]; cell survival following a 1-h exposure was measured using a soft-agar colony assay. A similar dose-response curve was obtained with melphalan for each of the 4 xenografts, despite previous treatment with an alkylating agent in two of the patients from whom the xenografts originated. Cell survival was also compared after JM8 and cisplatin exposure in each individual xenograft. It was found to be similar for each tumor when the concns. of JM8 used were 10-fold greater than those of cisplatin. Early clin. studies in which JM8 has been shown to be effective in the treatment of ovarian carcinoma support the view that xenograft tumors may have a role in phase-II screening of new cytotoxic agents.

Answer 37:

Bibliographic Information

Scheduling of chemotherapy and radiotherapy in locally advanced non-small cell lung cancer. Bishop J F Division of Haematology and Medical Oncology, Peter MacCallum Cancer Institute, East Melbourne, Victoria, Australia Lung cancer (Amsterdam, Netherlands) (1995), 12 Suppl 2 S53-61. Journal code: 8800805. ISSN:0169-5002. (CLINICAL TRIAL); (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RANDOMIZED CONTROLLED TRIAL); General Review; (REVIEW) written in English. PubMed ID 7551950 AN 96040350 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

In scheduling chemotherapy and radiotherapy for locally advanced non-small cell lung cancer (NSCLC), chemotherapy can be given pre-radiotherapy or concurrently as a single agent or in combination. Optimal scheduling has yet to be established. Optimal pre-radiotherapy for NSCLC requires further development but cisplatin with vinblastine, vindesine, etoposide or navelbine appear the best currently available. A number of new drugs show potential for enhancing radiation effects. Concurrent chemotherapy and radiotherapy has been tested in a number of experimental tumours in cell culture. In these systems cisplatin, carboplatin, 5-fluorouracil, mitomycin-C and other agents appear to improve cell kill compared to chemotherapy alone. Mouse xenograft models allow the study of various concurrent drug and radiation schedules including the effect of radiation with cisplatin, carboplatin, paclitaxel and gemcitabine. In these systems, cisplatin in divided doses shows optimal enhancement with fractionated radiotherapy. There are a number of drug candidates for concurrent chemotherapy and radiotherapy programs. Clinical studies in head and neck cancer, esophageal cancer, small cell lung cancer and NSCLC show promising results with concurrent chemotherapy and radiotherapy. Cisplatin given daily

with radiotherapy improved survival in NSCLC compared to cisplatin given weekly with radiotherapy or to radiotherapy alone. To study the toxicity of radiation and concurrent carboplatin, we have studied 170 patients with unresectable locally advanced NSCLC in a 4-arm randomized trial. An analysis of the first 100 patients entered revealed significantly more neutropenia ($P < 0.0001$) and thrombocytopenia ($P < 0.004$) with the combined modality arms. Esophagitis was worse on all three experimental arms but was significantly more prolonged with accelerated radiotherapy arms.(ABSTRACT TRUNCATED AT 250 WORDS)

Answer 38:

Bibliographic Information

Chemotherapy of human carcinoma xenografts during pulsed magnetic field exposure. Hannan C J Jr; Liang Y; Allison J D; Pantazis C G; Searle J R Radiology Department, Medical College of Georgia, Augusta 30912 Anticancer research (1994), 14(4A), 1521-4. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 7979179 AN 95069897 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Immune deficient mice growing xenografts of HT-29 or A-431 cell lines were treated with cisplatin, carboplatin or doxorubicin in combination with one hour of wholebody pulsed magnetic field (PMF) exposure (calculated peak field 5.2 mTesla, with an average field strength of 0.525 mTeslarms; pulses rose for 120 microseconds and then abruptly fell to neutral, and were repeated at a rate of 250 pulses per second). At 24 days, the mice in each experiment were found to have significantly ($p < 0.05$, ANOVA) different tumor sizes among groups. The smallest mean tumor volume was consistently found in the drug+PMF group. With A-431 tumors, the cisplatin+PMF group (T) was significantly smaller, 52% [1-(100T/C)], than the cisplatin alone group (C). In HT-29 tumors, those treated with carboplatin+PMF had the smallest tumor volume at just 34% of the carboplatin-alone group. In HT-29 tumors, the doxorubicin+PMF group was 35% of the doxorubicin alone group.

Answer 39:

Bibliographic Information

Anti-cancer drug sensitivity test against human testicular cancer xenograft--comparison with clinical results of chemotherapy. Miki T; Kotake T Center for Adult Diseases, Osaka Hinyokika kiyo. Acta urologica Japonica (1988), 34(11), 1903-9. Journal code: 0421145. ISSN:0018-1994. (COMPARATIVE STUDY); (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 3242364 AN 89205232 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The antitumor effect of vinblastine (VBL), vincristine (VCR), etoposide (VP-16), teniposide (VM-26), cisplatin (CDDP), CBDCA (JM-8, Carboplatin), CHIP (JM-9), DWA2114R and recombinant human tumor necrosis factor (TNF) on four human testicular cancers heterotransplanted in nude mice were studied. The treatments with CDDP, CBDCA or CHIP significantly reduced the transplanted tumors. Combination chemotherapy with CDDP, bleomycin and VBL or VCR or VP-16 or VM-26 also revealed significant tumor regression. The antitumor effect of TNF on human testicular xenografts was much more evident when it was given intratumorally than when given intravenously. Teratoma was resistant to TNF even when it was administered intratumorally. Those results are briefly discussed and compared with the clinical results of chemotherapy. Several problems in anticancer drug sensitivity test against human tumor xenografts are also discussed.

Answer 40:

Bibliographic Information

Antitumor activity of cisplatin and carboplatin against human tumor xenografts serially transplanted into nude mice--with special reference to gastric carcinomas. Shimoyama Y; Kubota T; Inoue S; Kuzuoka M; Ohishi T; Oka S; Kikuyama S; Ishibiki K; Abe O Gan to kagaku ryoho. Cancer & chemotherapy (1987), 14(9), 2682-7. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 3307633 AN 87324953 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Experimental chemotherapy with cisplatin and carboplatin was performed against nine human tumor xenografts serially transplanted into nude mice. Tumors used for the experiment were seven gastric (St-4, St-15, St-40, H-111, SC-2-JCK, SC-6-JCK and Exp-4), one breast (MX-1) and one colon (Co-4) carcinomas. Cisplatin 9 mg/kg and carboplatin 100 mg/kg were administered intraperitoneally (ip). Carboplatin 25 mg/kg was also given ip 4 times every 4 days. The efficacy rates of cisplatin and carboplatin by bolus injection were 77.8% and 66.7% respectively with no statistically significant differences. However, carboplatin was found more effective when given by bolus. The antitumor spectra of both drugs were similar. From these results, these two platinum compounds seemed to be effective against human gastric carcinomas.